REMARKS

Applicant appreciates the Examiner's thorough consideration provided the present application. Claims 1, 7, 9, 11, 12, 15, 16, 23, 24, 27, 29, 36, 37, 44 and 47-51 are now present in the application. No claims have been amended in this Reply. Claims 1 and 29 are independent. Reconsideration of this application is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

Claims 1, 7, 9, 11, 12, 23, 24, 27 and 48 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Malin, U.S. Patent No. 5,377,002, in view of Hamashima (U.S. Patent No. 4,744,663). Claims 15 and 16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Malin in view of Hamashima, and further in view of Worster (U.S. Patent No. 5,479,252). Claims 29, 36, 37, 47 and 49-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Malin in view of Hamashima, and further in view of Dixon (U.S. Patent No. 5,381,224). Claim 44 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Malin in view of Hamashima, and further in view of Raz (U.S. Patent No. 6,049,421).

Independent claim 1 recites a combination of elements including "[a]n apparatus for identifying a position of marked objects having unknown positions and detecting a property of the marked objects contained in a specimen, wherein the marked objects are marked with a fluorescent stain, the apparatus comprising a frame, a member positioned on the frame and having a surface that is adapted to receive and hold the specimen, at least a first light source for emitting at least a first light beam towards the specimen held by the member, wherein the first light beam is adapted to provide a light spot having a diameter between 20-150μm on the

specimen, at least a detector for detecting fluorescent light emitted from the marked objects upon interaction with the first light beam, the first light source and the detector being arranged so that a part of a light beam path from the first light source to the specimen is co-axial with a part of the light emitted from the marked objects, at least one beam-splitter being arranged to reflect the first light beam towards the specimen and filter light emitted from the specimen, thereby allowing fluorescent light from the marked objects to pass through the beam-splitter to the detector, scanning means for scanning the entire surface of the member in relation to the detector along a non-linear curve, wherein the scanning means comprises means for rotating the member and means for displacing the member along a radius of the rotation of the member, so as to identify the position of the marked objects in the entire specimen and detect the property of the marked objects, the means for rotating and the means for displacing being directly connected to the member, the member being rotatable and displaceable along a radius of the rotation of the member, scanning control means for controlling the scanning means for scanning the specimen along the non-linear curve, storage means for storing detector signals relating to the marked objects provided by the detector and corresponding position signals provided by the scanning control means, means for retrieving the position signals stored in the storage means, and a microscope for viewing images of the marked objects, wherein the scanning control means use the retrieved position signals to place the microscope at the position of the marked objects to allow performing a detailed examination of the marked objects."

Independent claim 29 recites a combination of steps including "[a] method of identifying a position of a fluorescently marked object having an unknown position and detecting a property of the object contained in a specimen, wherein the object is a biological cell or a microorganism,

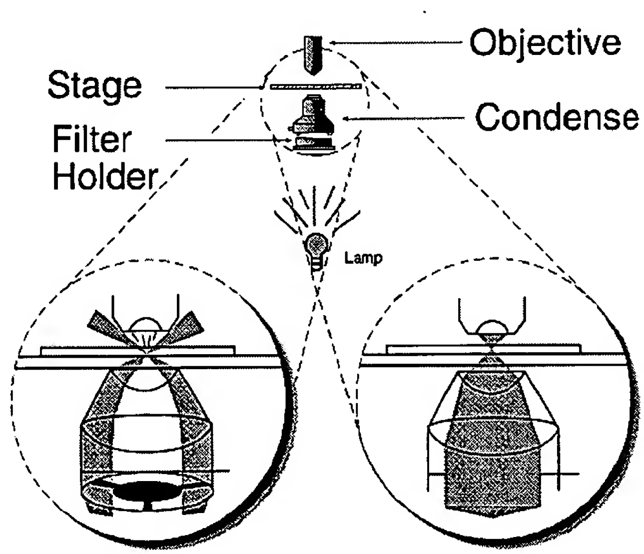
the method comprising the steps of: positioning the specimen on a member having a surface that is adapted to receive and hold the specimen, emitting at least a first light beam from a first light source towards the specimen held by the member, wherein the first light beam is adapted to provide a light spot having a diameter between 20-150μm on the specimen, and wherein the first light beam is reflected by a beam-splitter towards the specimen, scanning the entire surface of the member in relation to a detector along a non-linear curve by rotating the member holding the specimen and displacing the member along a radius of the rotation of the member, the member being rotatable and displaceable along a radius of the rotation of the member, arranging the light source and the detector, so that a part of a light beam path from the first light source to the specimen is co-axial with a part of a light emitted from the object, filtering through said beam-splitter light emitted from the specimen, passing fluorescent light from the marked objects through the beam-splitter towards the detector, detecting the fluorescent_light emitted from the object, thereby identifying the position of the object and detecting the property of the object during scanning of the entire specimen, storing detector signals relating to the object provided by the detector and corresponding position signals provided by the scanning control means, retrieving the position signals stored in the storage means, placing a microscope at the position of the object using the retrieved the position signals to allow performing a detailed examination of the object, and optically inspecting the object by viewing an image of the object via the microscope by a user."

Applicant respectfully submits that the above combinations of elements and steps as set forth in independent claims 1 and 29 are not disclosed nor suggested by the references relied on by the Examiner.

Malin

Malin relates to examination and inspection of surfaces for defects and contamination using a dark field microscopy. This allows for having higher resolution as well as greater measuring sensitivity (col. 2, lines 20-22). However, Malin does not relate to detection of fluorescent light. Applicant respectfully requests that the Examiner focus on the difference in the principle of operations of Malin and the claimed invention and also on the inapplicability of Malin to detect fluorescence.

Principles of Operation & Inoperability with Fluorescence



Darkfield **Brightfield**

The darkfield microscopy relies on an illumination system where a stop is used to form a hollow cone of light. The light at the apex of the cone is focused at the plane of the specimen. As this light moves past the specimen plane, it spreads again into a hollow cone. When a sample is on the stage, the light at the apex of the cone strikes it. *The image is made only by those rays scattered by the sample and captured in the objective lens.* Scattering light includes the light deflected haphazardly as a result of collision with defects and contaminations on the surface. As a result, the angle of the scattering light is anything but perpendicular to the surface, which is why the dark field stop in fact works when studying scattering, because the scattering light

diverges past the dark field stop. *Darkfield illumination minimizes the quantity of directly-transmitted (un-scattered) light entering the image plane, collecting only the light scattered by the sample.* This is illustrated in Figs. 4a-4c and col. 5, line 48 – col. 6, line 23 of Malin, where it discloses that the implementation of a dark field stop is an essential part of the system. It is also clear from col. 6, lines 45-56 of Malin that any light having a path perpendicular to the surface of the object does not reach the detector, but is deflected towards the light source. As a consequence, a dark field stop in the light path will stop the light emitted from the fluorescently marked objects to a degree where detection becomes impossible. This is particularly the case when small objects like biological cells are under investigation.

In contrast, fluorescence microscopy is a <u>bright field</u> microscope and relies upon the light from the lamp source being gathered by the sub-stage condenser and shaped into a cone whose apex is focused at the plane of the specimen. The fluorescence in the specimen gives rise to emitted light which is focused perpendicularly to the detector. The emission is spherical and a sufficiently large receiving aperture is used in order to collect as much light from the fluorescently marked objects, when the amount of fluorescent light is limited.

Therefore, although there are some structural similarities between Malin and the claimed apparatus, the principle of operation in Malin teaches away from that in the claimed invention because Malin uses a <u>dark field stop</u> as an essential element. This not only restricts any possible detection of fluorescence but also leads a skilled person in a direction divergent to the claimed invention.

Limitation Imposed by Fluorescent Stain

In the outstanding Office Action, the Examiner states the recitation "wherein the marked objects are marked with a fluorescent stain" was not given any patentable weight since the object marked by a fluorescent stain is not a component of the claimed apparatus and does not appear to impose any additional structural limitations on the claimed apparatus. Based on the above-noted arguments that Malin cannot be used for detecting fluorescent stain due to the presence of the dark field stop which inherently stops light emitted from a fluorescent stain in the objective, Applicant respectfully submits that this feature does in fact impose an additional structural limitation to the claimed apparatus.

Spot Size

The Examiner further states that Malin suggests a light spot diameter of more than 1 μm. However, Malin does not teach a light spot diameter between 20-150 μm. Malin may teach something which is larger than 1 μm. However, the claimed invention relates to a light spot being at least 20 times larger which cannot be read into Malin. The Examiner allows himself to extract from Malin that a light spot of 50 μm is taught without any substantiated basis for such a statement.

In addition, MPEP 2144.05.II.B states as follows:

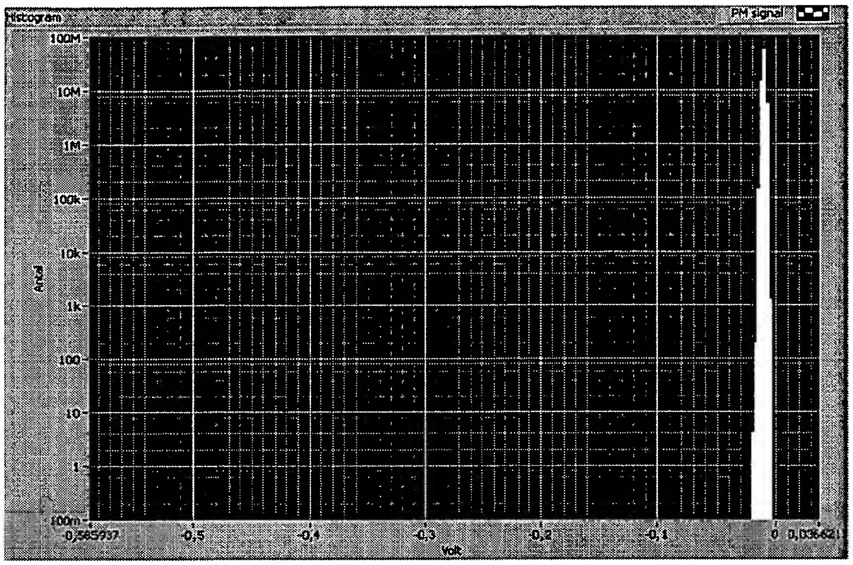
> ***B. Only Result-Effective Variables Can Be Optimized***
> <u>A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation</u>. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not

> recognized in the art to be a result- effective variable.). See also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy). (Emphasis added).

Here, the spot diameter in the present invention is critical because it is adapted to a particular application so that an optimum signal to noise ratio is provided in the detector signal, thereby enhancing the discrimination between target objects and false positive signals. This variation in the spot diameter becomes even more critical when the fluorescence emitted by small sized marked object is relatively weak. *Malin is silent about enhancing the signal-noise ratio using the spot diameter*. In other words, *Malin fails to recognize the spot size as a result-effective variable to enhance the signal-noise ratio*. The spot measurement of Malin would not provide any suggestion to a person skilled in the art, and therefore the skilled person could not have modified the size of the spot diameter to improve signal to noise ratio and to cover the range claimed in the present invention. Therefore, the spot taught in Malin et al. cannot be regarded as a result-effective variable.

In view of the above, Malin not only teaches away from the claimed invention and has inoperability limitation to measure fluorescence emissions, as evidenced by experimental data, but also fails to address the issue of signal-noise ratio and recognize the spot size as a result-effective variable to enhance the signal-noise ratio. Therefore, the claimed invention is non-obvious over Malin and Malin is not a relevant reference for combination with any other art because of fundamentally opposite principle of operation in comparison to the one used in the present invention.

Hamashima



Signal corresponding to an n.a. on 0.6 (The Hamashima configuration)

Hamashima discloses a pattern position detecting apparatus using a laser beam which is used for the recognition of an edge position. To find edges in a pattern, which is the purpose in Hamashima, both of the scattered light and a fluorescent signal are needed. There is a need to include several optical systems in Hamashima, making it impossible to bring any conclusion from the cited art to the claimed invention. The light scatter is arranged in a kind of ring optics, while the fluorescent signal is detected by the transmitting optics. In order to provide sufficient physical space for the ring optics, the working distance of the objective must be increased significantly, resulting in a reduction of the numerical aperture and, therefore, a reduced signal level. A small area device, as described in the present invention, will not lead to any signal in Hamashima set up, as signal reduction on 10 dB will come with a numerical aperture (n.a.) even at 0.6 vs. the n.a. at 0.7 used today. This is demonstrated on the figure above, where a reduction

of the n.a. is performed by an iris diaphram. This figure is identical to Fig. 6 of a Declaration under 37 C.F.R. § 1.132 as filed concurrently herewith (see below), where the shutter is completely closed. This also shows that the Hamashima configuration will be unable to solve the problem, which is addressed by the present invention.

Despite the shortcomings of Hamashima, as mentioned above, the Examiner states that Hamashima teaches use of dichroic mirror for simultaneous detecting three kinds of light information. Therefore, it would have been obvious to a person skilled in the art at the time of the invention to provide a dichroic mirror as the at least one beam splitter and other optical components in the apparatus of Malin in order to obtain reflection, scattering and fluorescence measurements at a desired resolution.

Applicant respectfully submits that Hamashima discloses two different systems, namely, detection of edges by detection of light scattering back like in Malin, and detection of fluorescence from a pattern incorporated in a wafer. The two systems are incorporated in one apparatus but use separate light sources and separate detectors, *i.e.,* the light source 10 and the detector 36 and the light source 62 and the detector 60, respectively. Therefore, by combining Malin with Hamashima, one skilled in the art is taught that detection of fluorescence and detection of scattering are performed in two different systems. Therefore, one skilled in the art would not incorporate detection of fluorescence in the system setup of Malin.

More specifically, even if the Examiner's contention were taken into account, the dichroic mirror could be used either as an additional element or as a replacement of the dark field stop in the apparatus of Malin.

If the dichroic mirror is used as an additional component along with the dark field stop in the system of the primary citation, then the dichroic mirror would not collect the directly-transmitted light and therefore would not be reading over the claimed invention. Therefore, adding the dichroic mirror does not provide the apparatus of Malin with a possibility of detecting any fluorescent emission from the object, since such emission cannot pass the dark field stop, which is an essential part of Malin.

The Examiner in the outstanding Office Action states "[t]he test for obviousness is not whether the features of a secondary reference (Hamashima) may be bodily incorporated into the structure of the primary reference (Malin). Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." However, MPEP 2143.01.VI states as follows:

> **VI. THE PROPOSED MODIFICATION CANNOT CHANGE THE PRINCIPLE OF OPERATION OF A REFERENCE**
>
> If the proposed modification or combination of the prior art would <u>change the principle of operation of the prior art invention being modified</u>, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).... (Emphasis added).

Here, since Malin's system would cease to operate in the area of dark field microscopy if the dark field stop is replaced by a dichroic mirror of Hamashima, the proposed modification or combination of the prior art would change the principle of operation of Malin. Therefore, one of ordinary skill in the art would not have recognized the predictability of the result with Malin, which relies heavily on the use of dark field stop. Consequently, the teachings of the references are not sufficient to render the claims *prima facie* obvious.

Worster

The Examiner states that disclosure of wafer size ranging between 75 mm and 200 mm diameter in Worster would make the claimed specimen area of larger than 500 mm^2 obvious to a person skilled in the art, if the skilled person reads this teaching along with the teachings of Malin and Hamashima

Applicant respectfully submits that, since the teachings of Malin and Hamashima are not sufficient to render the claims *prima facie* obvious because the proposed modification or combination of Malin and Hamashima would change the principle of operation of the Malin being modified, the additional teaching of Worster will not render the claims *prima facie* obvious.

Dixon

The Examiner states that Dixon is capable of measuring both scattered light and fluorescence for both macroscopic semiconductor and macroscopic biological specimen. Therefore, it would have been obvious to the skilled person that the modified method claim of Malin can be used for both macroscopic semiconductor specimens and macroscopic biomedical specimens, which may also include fluorescently marked biological cells.

Applicant respectfully submits that, since the teachings of Malin and Hamashima are not sufficient to render the claims *prima facie* obvious because the proposed modification or combination of Malin and Hamashima would change the principle of operation of the Malin being modified, the additional teaching of Dixon will not render the claims *prima facie* obvious.

Further, the inclusion of teaching of Dixon with Malin only indicates that macroscopic biological material can be scanned for fluorescence emission. However, as mentioned, the presence of the essential element "dark field stop" in Malin prohibits detection of fluorescence emission. The apparatus of Malin remains unchanged even with the teachings of Dixon because with the dark field stop, Malin would not measure fluorescence. In addition, the apparatus of Malin cannot be modified as the Examiner alleged because the principle of operation of the combination is contradictory to that of Malin. Malin does not teach filtering through the beam splitter of the light emitted from the specimen. In addition, it has already been argued that the size of the spot diameter is not recognized as a result effective variable by the prior art. Therefore, the claimed invention includes features that are neither covered nor taught in a way that the skilled person would combine the utilized references with reasonable predictability to devise the present invention.

Raz

Although Raz discloses scanning a substrate using a CCD device, incorporation of the CCD into the apparatus of Malin would still leave the skilled person with the question of modifying the apparatus disclosed in Malin for fluorescence measurement. Such measurement is only possible if the dark field stop is not a part of Malin's apparatus. However, this would change the principle of operation of the disclosed Malin's apparatus. Therefore, the CCD device of Raz does not make the claims obvious.

Accordingly, none of the references utilized by the Examiner individually or in combination teach or suggest the limitations of independent claims 1 and 29 or their dependent

claims. Therefore, Applicant respectfully submits that claims 1 and 29 and their dependent claims clearly define over the teachings of the references relied on by the Examiner.

In addition, Applicant hereby respectfully submits a Declaration under 37 C.F.R. § 1.132 from an expert demonstrating whether fluorescence can be detected in a dark field microscopy of Malin and whether the inclusion of a dichroic mirror, as suggested by the Examiner, is possible in the set up of Malin.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

Response To Examiner's Comments In Advisory Action

In the Advisory Action dated July 22, 2009, the Examiner stated that the arguments submitted with the Reply dated July 10, 2009 were not persuasive. In particular, the Examiner maintained his position based on the following grounds, followed by Applicant's arguments to respond to the Examiner's comments.

(1) Transmission geometry shown in the figure at page 12 of the July 10 Reply is inapplicable to the reflection geometry in Figs. 1 and 2 of Malin.

Applicant respectfully submits that the July 10 Reply showed that the excitation light path is reversed relative to the path described in Malin. However, equivalence principle in optics proves the equivalence between the two setups in principle, and therefore, the substitution of the reflective geometry with the transmission geometry is allowed in order to illustrate the effect of the dark field stop in the light collection.

The transmission geometry of the figure at page 12 of the July 10 Reply (and the figure at page 12 of this Reply) describes the operating principle of dark field microscopy and its limitation in detecting the fluorescence because of the presence of the dark field stop. Because of the equivalence principle, Malin's reflective geometry based dark field system will still show the same limitations, which are introduced by a dark field stop in a transmission geometry based dark field system. Therefore, the limitation of the dark field microscopy is not a function of transmission or reflection geometry. Instead, it depends on whether the system represents a bright field microscopy or a dark field microscopy using a dark field stop. Applicant respectfully submits that the Examiner is erroneously relying on a scientific theory, according to which he considers that the limitation of dark field microscopy depends on the geometry rather than the use of the dark field stop. Therefore, the geometry based rejection lacks evidentiary evidence. This is contradictory to the decision as laid down in *In re Grose,* 592 F.2d 1161, 201 U5PQ 57 (CCPA 1979), which states "when an examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory must be provided."

(2) Dark field illumination where a stop is used to block excitation light is inapplicable.

The reflective geometry and use of narrow light beam of Malin is the reason why the dark field stop was not included to block the excitation light in Malin. If the stop were placed in the path of the excitation light beam, the reflective geometry of Malin's system would block the light beam (1, a narrow light) from reaching the sample plane. This would make Malin's system inoperable because in absence of the light beam reaching the sample surface, there would not be any reflection from the surface of the sample plane. Therefore, instead of using the dark field in

the path of the excitation light beam, the stop is placed in the reflection light path to block a portion of light from the sample, resulting in detection of only the scattered light with high resolution, as intended in Malin.

Although the July 10 Reply discloses use of the dark field stop in the excitation light path, the effect at the detector of the stop placed to block either the excitation light or a portion of the light reflected from the sample would be same because both the figure at page of the July 10 Reply and Malin represent dark field microscopy and work on the same dark field microscopy principle. Therefore, for analysis and experimentation purposes, the figure at page 12 of the July 10 Reply is equivalent to Malin's system.

Therefore, the arguments presented based on the figure at page 12 of the July 10 Reply, as manifested by a stop in the excitation light path are applicable on Malin's system having the stop blocking the light from the sample. To disregard this argument and to conclude that the placement of the stop to block excitation light is functionally not equivalent to blocking a portion of the light from the sample, the Examiner should provide evidentiary evidence (see *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979)).

<u>(3) Unsupported argument about size of the dark field stop.</u>

The Examiner's position is based on Malin's statement "to allow passage of **diffused light** close to the optical axis, that proportion of the diffused-light cone 14 effectively blocked by the dark-field stop 61 must be as small as possible" (see col. 7, lines 10-14). Malin does not make any clear and unambiguous suggestion regarding the size of the dark stop. In fact, Malin is only directing a skilled person in the art towards detection of "diffused light", rather than

fluorescence. Moreover, there is not even an implicit reference in the prior art relied on by the Examiner regarding detection of fluorescent light.

Consequently, even if the prior art relied on by the Examiner were to indicate that the passage of diffused light should be close to the optical axis, the prior art relied on by the Examiner cannot be relied on to have reasonably suggested to one having ordinary skill in the art the specific size of the dark field stop and the possibility of detection of the fluorescence from the sample in the presence of the dark field stop. Furthermore, because of general property of dark field stop to minimize the quantity of directly-transmitted, fluorescence would not be detected. Therefore, Applicant respectfully disagrees with the Examiner's observation.

(4) Malin in combination with Hamashima.

The above arguments in combination with the July 10 Reply clearly demonstrate that Malin is not applicable prior art to question the inventiveness of the present invention. Additional teachings of Hamashima do not overcome the limitations introduced by the dark field stop in Malin's system. Removing the dark field stop from Malin's system and combining such system with the teachings of Hamashima are improper because the proposed modification would change the principle of operation of the Malin's system. (see *In re Ratti,* 270 f. 2d 810, 123 USPQ 349 (CCPA 1959).

In addition, the Examiner has not commented on all the arguments presented in the July 10 Reply. In particular, the present invention is further non-obvious because of the arguments presented at pages 13-15 of the July 10 Reply (and this Reply) in support of "Limitation Imposed by Fluorescent Stain" and "Spot Size." Applicant respectfully submits that the above arguments

were presented in good faith and deserve to be considered and responded to on their merits in the next Office Action.

CONCLUSION

It is believed that a full and complete response has been made to the Office Action, and that as such, the Examiner is respectfully requested to send the application to Issue.

In the event there are any matters remaining in this application, the Examiner is invited to contact Cheng-Kang (Greg) Hsu, Registration No. 61,007 at (703) 205-8000 in the Washington, D.C. area to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant respectfully petitions for a two (2) month extension of time for filing a response in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: August 11, 2009

Respectfully submitted,

By #61007

Paul C. Lewis
Registration No.: 43,368
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road, Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

Attachment: Declaration under 37 C.F.R. § 1.132